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GB 1553310 US 4017641
EP A1 0006724 US 3969516

(58) Field of search
A5B

(54) Pharmaceutical compositions for percutaneous administration

(57) A pharmaceutical composition for administration to the skin comprises a pharmaceutical agent, such as a benzodiazepine, and a percutaneous carrier liquid comprising:

(A) a compound melting at below 38°C which is a C5—24 aliphatic hydrocarbon optionally halo-substituted, a C7—18 ester of an aliphatic carboxylic acid, a C10—18 ether, a C11—15 ketone, or a 10—26C aliphatic monoalcohol which may be unsaturated or cyclic, provided that if it is 14—26C it has at least one unsaturation, branched chain and/or alicyclic group;

(B) a thioglycerol, lactic acid or ester, cyclic urea, alkyl or acyl urea, alkyl amide and/or pyrrolidone or N-alkyl pyrrolidone; and

(C) a diol, preferably C3—8.

The weight of (A) is 0.1—80% of (A)+(B); the weight of the pharmaceutical agent is 0.01 to 50% of (A)+(B); the diol (C) is preferably 10—100 wt% of (B).

The diol (C) reduces the effect of (A) and (B). Other components or vehicles can be present. The agent is rapidly absorbed through the skin of a mammal to which the composition is applied.

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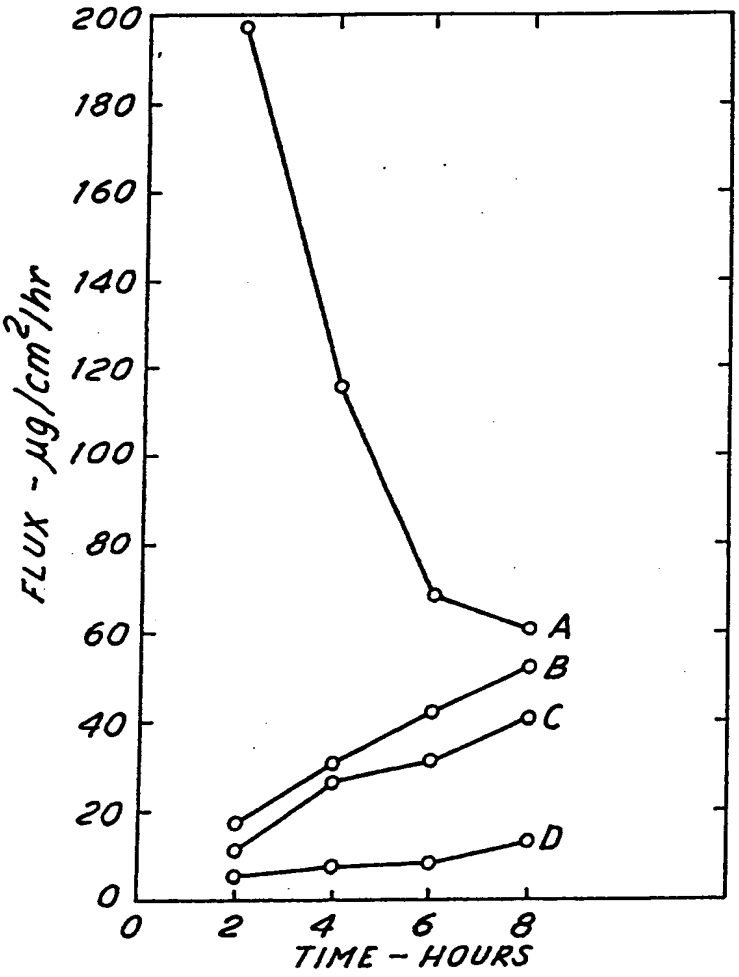


IN VITRO DIAZEPAM FLUX THROUGH RAT SKIN AT 30°C

SPECIFICATION

Pharmaceutical Compositions for Percutaneous Administration

The present invention relates to pharmaceutical compositions which include a carrier composition for accelerating the percutaneous absorption of a physiologically active or pharmaceutical agent (the latter is often merely described herein as an "active agent" for brevity) from the compositions.

Active agents are commonly administered to the skin or mucosal tissues to treat local problems and systemic administration of active agents is commonly accomplished by ingesting pills or by injections. However, recently attempts have been made to achieve systemic administration of active agents by topical applications to the skin or mucosal tissues. Such topical means of achieving systemic administration has the advantage that desired blood levels can be readily achieved and maintained so that duration of therapy can be readily controlled. Thus, side effects due to an overdose of the active agent can be prevented. Also, metabolism due to a first pass through the liver and gastric disturbances, which are characteristic of certain drugs such as indomethacin when administered orally, can also be eliminated.

However, normal skin is relatively impermeable to most therapeutic agents in that desired blood levels of the therapeutic agent cannot be achieved by means of percutaneous absorption. The percutaneous absorption of therapeutic agents can, however, be enhanced by means of adjuvants or penetration enhancers.

One of the best known of such penetrating adjuvants is dimethyl sulfoxide, the use of which is described in detail in U.S. Patent 3,551,554 Herschler et al, which patent broadly suggests the use of dimethyl sulfoxide as a penetrating adjuvant for psychopharmacological drugs such as benzodiazepine derivatives.

British Patent 1,504,302 Brooker et al discloses sedative methods and compositions and discloses the administration of sedatives by applying to the skin of a non-human animal a sedating amount of one or more sedative compounds in various penetrating adjuvants such as hydrocarbons such as aromatic hydrocarbons or paraffins, halogenated aliphatic hydrocarbons, ketones, esters, ethers, alcohols, amides or sulfones. Brooker et al broadly indicates that one or more of the above liquids can be used in combination, but exemplify the halogenated aliphatic hydrocarbons only with carbon tetrachloride and exemplify the amides only with dimethylformamide.

Japanese Patent Application (OPI) No. 148,614/77 Yonemushi discloses, without supporting data or explanation of substance, the use of sulfones by-produced in the refining of petroleum "as solvents to enhance the efficacy of drugs for skin disease" and "as drug penetration enhancers".

U.S. Patent 4,202,888 Eckert et al discloses absorbable pharmaceutical compositions comprising at least one cardiac glycoside distributed in a vehicle comprising an absorption-enhancing amount of at least a partial glyceride of a fatty acid of medium chain length.

U.S. Patent 3,472,931 Stoughton relates to percutaneous absorption using lower alkyl amides, and exemplifies binary systems which comprise dimethylacetamide and ethanol, dimethylacetamide and isopropyl alcohol and dimethylacetamide and isopropyl palmitate. Stoughton does not exemplify or disclose the combination of dimethylacetamide with higher molecular weight alcohols or lower molecular weight esters.

U.S. Patent 4,017,641 DiGiulio discloses skin moisturizing compositions comprising 2-pyrrolidones which can be used with suitable oils and waxes including aliphatic straight chain fatty acids and alcohols of from about 10 to about 20 carbon atoms. This patent does not, however, deal with percutaneous administration of physiologically active agents.

European Patent Application 0043738 discloses binary percutaneous administration systems which comprise a monoglyceride, a diol or a diol ether in combination with a second component such as an alcohol, ester, amide or the like.

The present invention involves multicomponent carrier systems for the percutaneous administration of physiologically active agents which differ from the systems disclosed in the above prior art.

In the present invention, it has been discovered that certain multicomponent carrier systems provide enhanced and controlled percutaneous administration of physiologically active agents.

The carrier systems of the present invention comprise at least one adjuvant (Component A), at least one solvent (Component B) and at least one diol (as a "moderator").

The adjuvants of the present invention are selected from aliphatic hydrocarbons or halogen substituted aliphatic hydrocarbons, alcohol esters of aliphatic carboxylic acids, mono- or di-ethers, ketones, higher aliphatic monoalcohols or mixture thereof. It is necessary that the adjuvant of the present invention have a melting point below 38°C.

The solvents of the present invention are selected from thioglycerols, lactic acid or esters thereof, cyclic ureas, compounds represented by the general formula $R_1R_2NCONR_3R_4$, pyrrolidone-type compounds, amides, lactones or mixtures thereof, each as defined more specifically below, or mixtures thereof.

Compositions containing the aforesaid components A and B are together described in our prior copending applications Nos. 8412569 and 8415975 (U.S. Ser. Nos. 496,732 and 510,133).

A composition of the present invention comprises a physiologically active agent dissolved in a mixture of Component A, Component B and a diol moderator. The composition can be applied to the skin.

The above-described compositions can be used as bases for medical preparations comprising active agents applicable to the skin.

One object of the present invention is to provide base compositions or percutaneous absorption enhancing combinations (often abbreviated as PAEC or PAECs hereafter) for medical preparations for external use which enhance the permeability of active agents through the skin and the percutaneous absorption of active agents.

A second object of the present invention is to provide pharmaceutical compositions comprising a PAEC for external use which provides good permeability of active agents through the skin and percutaneous absorption of active agents.

A third object of the present invention is to provide a method for enhancing the permeability of active agents through the skin and percutaneous absorption of active agents using a PAEC.

A fourth object of the present invention is to provide PAECs which ensure rapid and controlled transepidermal delivery of physiologically active agents in man or other animals.

A fifth object of the present invention is to provide such rapid and controlled transepidermal delivery which provides drug blood levels in the therapeutic range for the treatment of humans and other animals.

A sixth object of the present invention is to provide, through transepidermal delivery, at appropriately adjusted rates, relatively constant therapeutic blood levels so as to avoid the side effects and reduced therapeutic effects that may result from wide fluctuations in blood levels over time.

Examples of Component A include the following compounds.

(1) Straight, branched or cyclic aliphatic hydrocarbons having 5 to 24 carbon atoms which may be substituted with one or more halogens.

As halogen substituents, bromine and chlorine are preferred.

Straight or branched hydrocarbons having 5 to 24 (preferably 6 to 18) carbon atoms can be used which may be saturated or unsaturated with preferably 1 to 2 unsaturated bonds. In the case of cyclic hydrocarbons, 6 to 10 membered mono- or 10 to 12 membered di-cyclic hydrocarbons are preferred and such may be substituted with saturated or unsaturated alkyl groups having 1 to 4 carbon atoms such as methyl, butyl and isopropenyl.

Specific examples include *n*-pentane, *n*-hexane, *n*-heptane, *n*-octane, *n*-nonane, *n*-decane, *n*-undecane, *n*-dodecane, *n*-tetradecane, *n*-hexadecane, *n*-octadecane, 2-methylpentane, 2-methylhexane, 2,3-dimethylhexane, 2-methylnonane, 2,6-dimethyloctane, 2,2,4,4,6,8,8-heptamethylnonane, pristane, limonene, hydrogenated limonene dimer, cyclohexane, 1,3-dimethylcyclohexane, cyclooctane, isobutyl-cyclohexane, cyclododecane, methyldecaline, decaline, octyl chloride, decyl chloride, dodecyl chloride, hexadecyl chloride, dodecyl bromide and dichlorododecane.

(2) Alcohol esters of aliphatic carboxylic acids having a total number of carbon atoms of from 7 to 18, preferably 7 to 17:

As the alcohol moiety, monovalent alcohols having 1 to 6 carbon atoms such as methyl alcohol, ethyl alcohol, *n*-propyl alcohol, *iso*-propyl alcohol, *n*-butyl alcohol, *iso*-butyl alcohol, *sec*-butyl alcohol, *t*-butyl alcohol, *n*-amyl alcohol, *iso*-amyl alcohol, *n*-hexyl alcohol, etc., are preferred. Further, as the carboxylic acid moiety, fatty acids having 6 to 16 carbon atoms are preferred and saturated fatty acids having 8 to 14 carbon atoms are most preferred. Specific examples of such esters include methyl laurate, ethyl laurate, butyl laurate and isopropyl myristate.

(3) Mono- or di-ethers having 10 to 18 carbon atoms:

Specifically, there are alkyl monoethers such as dihexyl ether, dioctyl ether, methoxydodecane, ethoxydodecane, etc., ethers having an alicyclic group such as 1,8-cineole, etc., alkyl diethers such as ethlene glycol dibutyl ether and ethylene glycol dioctyl ether.

(4) Ketones having 10 to 18 carbon atoms:

Aliphatic ketones are preferred, examples of which include 2-undecanone, 3-undecanone, 4-undecanone, 5-undecanone, 6-undecanone, 2-dodecanone, 4-dodecanone, 5-dodecanone, and 7-tridecanone.

(5) Higher aliphatic monoalcohols having from 10 to 26 carbon atoms which may be branched, straight chain, saturated, unsaturated or cyclic and which may be primary, secondary or tertiary.

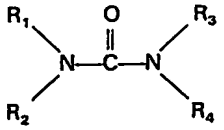
Examples of Component B include the following compounds:

(1) Thioglycerols:
Any mono-, di- and trithioglycerols can be used, an example of which includes α-monothioglycerol.

(2) Lactic acid and esters thereof:
As the alcohol moiety in the esters, monovalent aliphatic alcohols having 1 to 4 carbon atoms are preferred, specific examples of which include lactic acid, methyl lactate, ethyl lactate, butyl lactate, etc.

(3) Cyclic ureas:
5-Membered or 6-membered rings are preferred, specific examples of which include ethylene urea, N,N-dimethylethylene urea and the corresponding propylene ureas, etc.

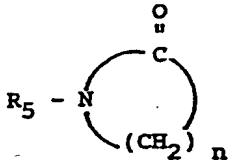
(4) Compounds represented by the general formula:



(I)

wherein R_1, R_2, R_3 and R_4 each represents a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms (methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc.) or an acyl group having 1 or 2 carbon atoms:
Specific examples thereof include urea, N-methylurea, N-ethylurea, N-butylurea, 1,1-dimethylurea, 1,3-dimethylurea, 1,1,3,3-tetramethylurea, N-acetyl-N'-methylurea, etc.

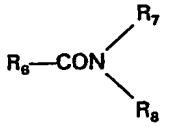
(5) Compounds represented by the general formula:



(II)

wherein R_5 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms (methyl, ethyl, *n*-propyl, *iso*-propyl, etc.) and *n* represents an integer of 3 to 5:
Specific examples thereof include 2-pyrrolidone, N-methyl-pyrrolidone, N-methylpiperidone, caprolactam, N-methylcaprolactam, etc.

(6) Compounds represented by the general formula:



(III)

wherein R_6 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms (methyl, ethyl, *n*-propyl, etc.) and R_7 and R_8 each represents an alkyl group having 1 to 3 carbon atoms, with the proviso that R_6, R_7 and R_8 have in total at least 3 carbon atoms:
Specific examples thereof include N,N-diethyl formamide, N,N-dimethylacetamide, N,N-diethylacetamide, N,N-dimethylpropionamide, N,N-diethylpropionamide, etc.

(7) Lactones having 4 to 6 carbon atoms:
Specific examples thereof include γ-butyrolactone, δ-valerolactone, etc.
As earlier indicated, a diol moderator is used in combination with the active agent and Components A and B in the present invention. The diol can be straight or branched chain and the diol selected is preferably a diol comprising 3 to 8 carbon atoms, most preferably 3 to 6 carbon atoms, e.g., an aliphatic diol such as 1,2-propane diol, 1,3-butane diol, 2,3-butane diol, 1,5-pentane diol or 1,6-hexane diol. However, other diols can be used.
The amount of diol moderator used is not unduly limited, but is typically of the order of about 10 to about 400 weight percent, more preferably about 25 to about 200 weight percent, based on the weight of solvent Component B. The resulting combination of materials must, of course, be liquid.
The diol moderator reduces the activity of Components A and B of the present invention, and thus provides a means of further controlling the rate of active agent absorption.

Greater amounts of diol moderator decrease the rate of active agent flux while lesser amounts of diol moderator increase the rate of active agent flux as compared to greater amounts.

It is to be understood that the diol moderator does not enhance percutaneous absorption in the present invention, rather, in all amounts it reduces the rate of percutaneous absorption, which effect has not been suspected previously.

In addition to the above, there are certain most preferred PAECs in the present invention, and these are discussed below.

We are unsure why the most preferred combination of PAECs of the present invention offers enhanced percutaneous absorption; however, the data we have generated indicates that there is a synergistic effect between Components A and B which can be appropriately moderated, as desired, by varying the amount of diol moderator.

We consider that Component B such as the pyrrolidone compounds and amides to basically serve as solvents and the Component A such as the alkyl halides, fatty acid esters, higher aliphatic monoalcohols and aliphatic hydrocarbons to serve as adjuvants which enhance the solvating function of the solvent. We further believe that the solvents carry the active agent whereas the adjuvants open up the stratum corneum. We do not wish to be bound by these theories, and we merely use the terminology "solvent" and "adjuvant" to maintain a line of distinction between the two classes of materials which are mandatorily used in combination.

The most preferred adjuvants as Component A of the present invention include one or more members selected from alkyl halides, fatty acid esters, higher aliphatic monoalcohols, aliphatic hydrocarbons and mixtures thereof.

Of the alkyl halides, those having from 8 to 16 carbon atoms are most preferred, with chloride being the preferred halogen. Both alkyl bromides and iodides are potentially useful, but alkyl bromides and alkyl iodides tend to be unstable. Alkyl fluorides are also useful.

The alkyl moiety may be straight or branched chain, may be cycloaliphatic or unsaturated, e.g., alkanes and alkenes are useful.

The most preferred alkyl halides are later exemplified.

The aliphatic hydrocarbons most preferably have 10 to 18 carbon atoms. They may be straight or branched chain and may be cycloaliphatic or unsaturated, e.g., alkanes and alkenes are useful.

The fatty acid esters are conveniently represented by the formula R_9COOR_{10}, R_9 representing the acid moiety and R_{10} representing the alcohol moiety. It is most preferred that the total number of carbon atoms in R_9 and R_{10} be from 10 to 17.

R_9 and R_{10} may be linear, branched, saturated, or unsaturated.

Preferred higher monoalcohols are the aliphatic monoalcohols with from 12 to 24 carbon atoms. The aliphatic monoalcohols may be branched chain, straight chain, saturated, unsaturated or cyclic.

The most preferred solvents as Component B include the pyrrolidone-type compounds and the amides.

The pyrrolidones are most preferably alkyl pyrrolidones of the general formula (II) above where R_5 is an alkyl group containing up to 4 carbon atoms.

The amides are most preferably represented by the general formula (III) above where R_7 and R_8 are each an alkyl group with up to 3 carbon atoms.

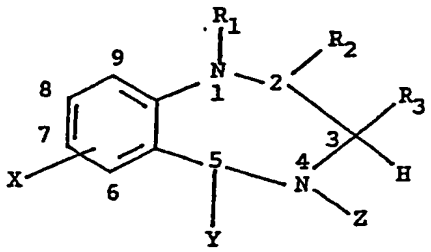
The base compositions in the present invention can be prepared by dissolving Component A in Component B and then mixing the diol moderator therein. The order of mixing is not important. The amount of Component A to be used is generally from 0.1 to 80% by weight based on the total weight of Components A and B, preferably 0.5 to 50% by weight. Preferred properties of diol moderator have earlier been given. Of course, pharmaceutically acceptable additives such as water, etc., can also be added to the base compositions.

The pharmaceutical compositions for topical application of the present invention can be prepared by blending active agents with the above-described composition. There is no particular limit on the active agents used so long as the active agents are systemically active and percutaneously applicable.

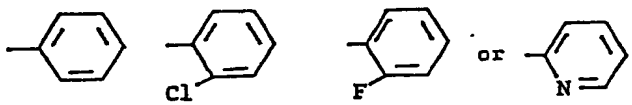
Specific examples of active agents include benzodiazepines (e.g., Diazepam, Nitrazepam, Flunitrazepam, Lorazepam, Fludiazepam, Clonazepam), diuretic agents [e.g., thiazides (e.g., Bendroflumethiazide, Polythiazide, Methyclothiazide, Trichloromethiazide, Cyclopenthiazide, Bentylhydrochlorothiazide, Hydrochlorothiazide, Bumetanide)], antihypertensive agents (e.g. Clonidine), antihistamic agents [e.g., aminoethers (e.g., diphenhydramine, Carbinoxamine, Diphenylpyraline), ethylenediamines (e.g., Fenbenzamine), monoamines (e.g., Chlorophenylamines)], non-steroid antiinflammatory agents (e.g., Indomethacine, Ibuprofen, Ibufenac, Alclofenac, Diclofenac, Mefenamic acid, Flurbiprofen, Flufenamic acid, Ketoprofen), anti-tumor agents (e.g., 5-fluorouracil, 1-(2-tetrahydrofuryl)-5-fluorouracil, Cytarabine, Floxuridine). Steroid antiinflammatory agents (e.g., Cortisone, Hydrocortisone, Prednisolone, Predonisone, Triamcinolone, Dexamethasone, Betamethasone), antiepileptic agents (e.g., Ethosuximide), antiarrythmic agents (e.g., Ajmalin, Purajmalin. Pindolol, Propranolol, Quinidine), psychotropic agents [e.g., Clofluperol, Trifluperidol, Haloperidol, Moperone), scopolamines (e.g., methyl scopolamine, butyl scopolamine), Metoclopramide, Chlorpromazine, atropines (e.g. methyl atropine bromide, methylanisotropine bromide), vascular dilating agents (e.g., isosorbide dinitrate, nitroglycerine, pentaerythritol tetranitrate, propanyl nitrate,

dipyridamole), antibiotics, e.g., tetracyclines (e.g., Tetracycline, Oxytetracycline, metacycline, doxycycline, Minocycline), chloramphenicols, erythromycines], etc. The method of the present invention can also be utilized to percutaneously administer peptides such as LH—RH, insulin and the like. Of course, pharmaceutically acceptable salts such as the hydrochloride, sodium, potassium, hydrobromide, etc., salts can be used.

Since the present invention is of particular application with respect to the benzodiazepine materials, these are discussed in more detail below. Particularly preferred benzodiazepine materials are those which have the benzodiazepine skeleton as schematically illustrated as follows:

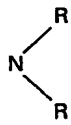


wherein X is Cl, Br, or NO_2 and Y is



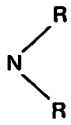
with varying degrees of unsaturation and substitution at positions 1, 2, 3, 4, and 5 as follows:

a) 1, 2 and 4, 5 are unsaturated: R_1 and R_3 are H; R_2 is

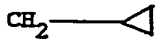


(R is H or CH_3) and N—Z is N→O.

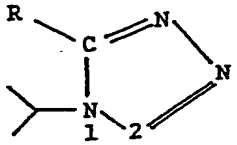
b) 1, 2 are saturated and 4, 5 are unsaturated: R_3 is H or OH; —R_2 is —H or =O or =N*; R_1 is



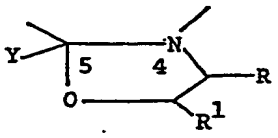
(R is H, CH_3 or



or CH_2—CH_2—$N(C_2H_5)_2$ or R_1 is C(R)=N* (R is H or CH_3) and is joined to R_2 via "*" (a single bond) as follows:



c) 1, 2 and 4, 5 are saturated: R_1 is H; —R_2 is =O; R_3 is H and positions 4 and 5 are part of a second ring system as follows:



where R and R^1 are H and CH_3.

Specific examples of benzodiazepines which can be percutaneously administered using the active ingredient/penetration adjuvant combinations of the present invention include:

a) Chlordiazepoxide;
7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide

b) Diazepam;
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one

c) Oxazepam;
7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepine-2-one

d) Temazepam;
7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-2H-1,4-benzodiazepine-2-one

e) Lorazepam;
7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepine-2-one

f) Prazepam;
7-Chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one

g) Fludiazepam;
7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepine-2-one

h) Flurazepam;
7-Chloro-1-(2-(dimethylamino)ethyl)-5-(*o*-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one

i) Medazepam;
7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-5,4-benzodiazepine

j) Bromazepam;
7-Bromo-5-(2-pyridyl)-3H-1,4-benzodiazepine-2(1H)-one

k) Nitrazepam;
1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepine-2-one

l) Nimetazepam;
1-Methyl-7-nitro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one

m) Clonazepam;
5-(*o*-Chlorophenyl)-7-nitro-1H-1,4-benzodiazepine-2(3H)-one

n) Flunitrazepam;
5-(*o*-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepine-2-one

o) Estazolam;
8-Chloro-1,6-phenyl-4H-s-triazolo(4,3-a)(1,4)-benzodiazepine

p) Triazolam;
8-Chloro-6-(*o*-chlorophenyl)-1-methyl-4H-s-triazolo(4,3-a)(1,4)-benzodiazepine

q) Alprazolam;
8-Chloro-1-methyl-6-phenyl-4H-s-triazolo(4,3-a)(1,4)-benzodiazepine

r) Oxazolam;
10-Chloro-2,3,5,6,7,11b-hexahydro-2-methyl-11b-phenylbenzo(6,7)-1,4-diazepino(5,4-b)-oxazol-6-one

s) Cloxazolam;
10-Chloro-11b-(*o*-chlorophenyl)-2,3,5,6,7,11b-hexahydrobenzo(6,7)-1,4-diazepino-(5,4-b)oxazol-6-one

t) Haloxazolam;
10-Bromo-11b-(o-fluorophenyl)-2,3,7,11b-tetrahydro-oxazolo(3,2-d)(1,4)benzodiazepine-6(5H)-one.

Especially preferred are benzodiazepines b), e), i), k), l), n) and o).

The amount of active agent(s) blended is sufficient if it is effective for achieving the desired pharmaceutical effect, which varies depending upon the kind of active agents, body weight of the patient, symptoms, etc. The amount may thus be suitably chosen depending upon these conditions. In general, it is preferred that active agents be employed in an amount of 0.01 to 50% by weight, more preferably 0.05 to 10% by weight, based on the total amount of Component A and Component B.

The dose of the active agents administered can be controlled by increasing or decreasing the area of skin to which the pharmaceutical compositions are applied. Accordingly, the amount of the active agent is not necessarily limited to the above-described ones.

As will be apparent to one skilled in the art, with increasing concentrations of active agent increasing amounts of active agent will be absorbed by the subject. The following discussion is given in terms of blood levels of drug (ng/ml of plasma), this being dependent upon the total area of dermal application, as there is a substantially linear increase in amount of active agent absorbed with area.

For a constant area of application and a constant absolute amount of adjuvant, the blood level of active agent at any given time is a function of the concentration of active agent in the composition. That is, increased concentrations of active agent in the formulation result in more rapid active agent penetration and higher blood levels.

A further factor which must be considered is that the amount of active agent absorbed will depend on the site of application, for example, scalp, ventral forearm, behind the ear, chest, etc. Typically an area rich in blood vessels is selected.

For most applications, the concentration of active agent in the PAEC will generally be of the order of 0.01 to 50% based on Components A and B, the amount of PAEC applied will be about 0.1 mg to 100 mg per cm^2 and the total area of application will be of the order of about 0.5 cm^2 to about 100 cm^2, which will provide therapeutic blood levels of the desired active agent.

These ranges are not, however, to be considered as limitative.

In general, the rate of transepidermal active agent absorption will approach the rate of oral absorption depending upon the factors previously discussed (nature and amount of PAEC, concentration of active agent in the formulation, and surface area of skin application). Thus, peak blood levels of the active agent may be reached more slowly or at about the same rate and will reach about the same level as those obtained by oral administration. Alternatively, the blood level of active agent attained by single dose oral administration may be maintained for an extended period by subsequent percutaneous administration of the active agent. In the latter case, the initial oral dose may be smaller than the normal therapeutic oral dose so that side effects associated with higher-than-minimal therapeutic blood levels attained by a reduced oral dose may be maintained by the subsequent transepidermal administration at a proper rate.

Therapeutic oral doses of Diazepam in man produce blood levels of approximately 100 ng/ml plasma [S. A. Kaplan, M. L. Jack, K. Alexander, and R. E. Weinfield, J. Pharm. Sci., *62*, 1789—1796 (1973)]. Such a blood level is easily attainable by percutaneous administration by way of the present invention and produces pharmacological (behavioral) signs of therapeutic effectiveness in appropriate animal models for man, e.g., the rhesus monkey.

The method of the present invention finds application with mammals in general, most particularly man and domestic animals such as cows, sheep, horses, dogs, cats and the like.

The pharmaceutical composition of the present invention is administered to the outer skin as a simple mixture or as a medical preparation by adding known pharmaceutically acceptable third components in the form of solutions, ointments (paste-including creams and gels) lotions, adhesive tapes, a plaster, etc.

For example, solutions may simply comprise the active agent dissolved in the PAEC with optional components, e.g., glycerin, and the solutions may be incorporated into absorbents, e.g., a gauze, porous membrane, etc.

Ointments, gels or creams may contain conventional ingredients (e.g., polyethylene glycol and hydroxy propylcellulose, etc.) to form the same, and the same may be spread onto backing materials, e.g., a plastic film.

Similarly, plasters or adhesives tapes may contain the active agent and PAEC in an adhesive base, e.g., acrylic copolymers or other synthetic gums.

The above listed components should essentially be inert in the system and not increase or decrease the effect of the PAEC.

The PAEC may be added to such a composition in varying amounts as desired, generally from 10 to 99% by weight.

In developing the present invention, we used both diffusion cells and an animal model. The diffusion cell methods provided a qualitative assessment of the active agent/PAEC effect on percutaneous absorption. The animal model rhesus monkey test also provides an acceptable pharmacokinetic model for man as indicated in J. Soc. Cosmet. Chem., 30, 297—307. Sept/Oct. 1979 and Toxicol. Appl. Pharmacol., 32, 394—398, 1975.

Experimental

In Vitro Skin Penetration Studies with Diffusion Cell Technique

Rat full thickness skins were used in the diffusion cell method of Michaels, AIChE Journal, *21* [5], 985—996, 1975. The rat skin was mounted in the diffusion cell in a vertical position between the upstream and the downstream compartments; the exposed area of the skin approximated 4.15 cm^2.

The skin was excised from the shaved abdominal site of male albino rats weighing 250~300 g, and washed with normal saline solution after the subcutaneous fat was carefully removed with scissors.

The active agent/PAEC solution of known concentration was added to the upper compartment of the cell, which was exposed to the epithelial side of the skin and a normal saline solution was placed in the lower compartment.

The penetration rate was studied in a thermostated bath at 30°C. At appropriate intervals samples were withdrawn from the lower compartment and subsequently analyzed for active agent concentration by standard analytical methods.

As an alternative, the finite dose technique of Franz, Curr. Probl. Dermatol., Vol. 7, p. 58~68 (Karger, Basel, 1978) can also be followed where the rat skin is mounted horizontally in a diffusion cell apparatus and the exposed area of the skin approximates 0.7 cm^2.

The active agent/PAEC solution of known concentration was added to the upstream

compartment to which the epithelial side of the skin was exposed, and a normal saline solution was added to the downstream compartment.

In Vivo Rhesus Monkey Test

If desired, an *in vivo* rhesus monkey test as described below can also be used to determine the effect of the PAEC/diol moderator combinations of the present invention.

Male rhesus monkeys weighing 10—14 Kg can be used as the subject. An appropriate area of the monkey's chest is shaved 24 hours before drug application.

Drug formulations comprising the PAEC are applied to a certain area of the chest. The monkey is restrained in a chair to prevent it from touching its chest.

Blood samples are taken at appropriate intervals after the application. The heparinized blood is centrifuged, and the plasma removed and stored at −20°C until analyzed.

Diazepam in plasma can be analyzed following the GLC method of Aingales, J. Chromatog., *75*, 55—78, 1973.

Hereafter the present invention will be illustrated with reference to Examples and to the single figure of the accompanying drawing, which is referred to in Example 1.

Compositions were prepared by firstly dissolving Component A with Component B, then mixing the active agent in the mixture and then mixing the diol therein. The order of mixing is not important. In the case that Component B is a solid at ambient temperature or will not homogenously mix with Component A, 20 wt. % of ethylene glycol monobutyl ether based on the weight of Components A and B was used as an agent for assisting dissolution.

Further, in the following examples, the abbreviations below are used:

$C_{12}OH$—dodecanol
$C_{12}Cl$—dodecyl chloride
DMAc—dimethyl acetamide
MP—1-methyl-2-pyrrolidone.

Unless otherwise indicated, in the following examples the active agent was Diazepam or metoclopramide hydrochloride. The flux of the active agent is given in the terms of $\mu g/cm^2/8$ hours. 25 Volume percent Component A with respect to component A and component B volume with or without diols was used in the composition together with 2.5 weight percent of the active agent. For purposes of comparison, in one instance the result for an adjuvant alone with a diol is given.

Example 1

The Figure is a graph of Diazepam flux versus time (in hours) illustrating the moderating effect of diols, for the systems: A) 25% $C_{12}Cl$ in DMAc (control), B) 25% $C_{12}Cl$ in a 1:1 weight mixture of DMAc/2,3-butane diol and C) 25% $C_{12}Cl$ in a 1:2 weight mixture of DMAc/2,3-butane diol. 25% $C_{12}Cl$ in 2,3-butane diol is also shown for comparison as curve D.

The drug concentration was 2.5% by weight in a ml reservoir.

Example 2

This example shows the moderating effect of diols for the systems $C_{12}OH$ in MP and 25% $C_{12}OH$ in a 1:1 volume mixture of MP/1,2-propane diol. Table 2 shows the metoclopramide HCl flux for 8 hours with these systems.

TABLE 2

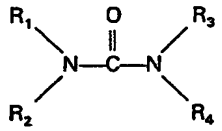
	Flux ($\mu g/cm^2/8$ hrs.)
25% $C_{12}OH$ in MP	4382
25% $C_{12}OH$ in a 1:1 volume mixture of MP/1,2-propane diol	1369

CLAIMS

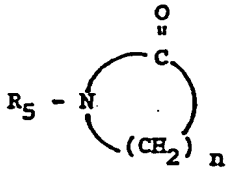
1. Pharmaceutical composition suitable for percutaneous administration which comprises a physiological active agent dissolved in a mixture of at least one of the following components A, at least one of the following components B; and component C:

Component A: straight, branched or cyclic aliphatic hydrocarbons having 5 to 24 carbon atoms, straight, branched or cyclic aliphatic hydrocarbons having 5 to 24 carbon atoms substituted with one or more halogen atoms, an alcohol ester of an aliphatic carboxylic acid having a total number of carbon atoms from 7 to 18, a mono or diether having 10 to 18 carbon atoms, a ketone having 11 to 15 carbon atoms, an aliphatic monoalcohol having from 10 to 26 carbon atoms provided that any monoalcohol containing more than 14 carbon atoms must contain at least one unsaturated bond, at least one branched chain and/or at least one alicyclic group in the molecule thereof; and mixtures thereof; having a melting point below 38°C;

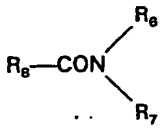
Component B: a thioglycerol, a lactic acid or an ester thereof, a cyclic urea, a compound represented by the general formula:



where R_1 to R_4 each represents a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, or an acyl group having 1 or 2 carbon atoms, a compound represented by the general formula:



wherein R_5 represents a hydrogen atom or an alkyl group having 1 to 4 carbon atoms and *n* represents an integer of 3 to 5, a compound represented by the general formula:



wherein R_6 represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms and R_7 and R_8 each represents an alkyl group having 1 to 3 carbon atoms, with the proviso that R_6, R_7 and R_8 have in total at least 3 carbon atoms, wherein Components A and B are present in an amount effective to enhance percutaneous administration of the active agent; and

Component C: a diol which is present in an amount effective to moderate the rate of percutaneous absorption of the active agent within the range of therapeutically effective rates.

2. A composition as claimed in Claim 1, wherein said diol has 3 to 8 carbon atoms.

3. A composition as claimed in Claim 2, wherein said diol is an aliphatic diol having 3 to 6 carbon atoms.

4. A composition as claimed in Claim 1, 2 or 3 wherein the diol is present in amount of 10 to 100 weight percent of Component B.

5. A composition as claimed in any preceding claim, together with additional carrier components to form a solution, ointment, lotion, adhesive tape, or incorporated into an absorbent vehicle.

6. A pharmaceutical composition as claimed in Claim 1, substantially as hereinbefore described with reference to any of the foregoing Examples.

7. A method of pharmaceutical administration to a mammal which comprises applying to the skin thereof a composition as claimed in any preceding claim.

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